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Steendam, Rob

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Document Version

Publisher's PDF, also known as Version of record

Publication date:
2005

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Steendam, R. (2005). *Amylodextrin and poly(DL-lactide) oral controlled release matrix tablets. Concepts for understanding their release mechanisms*. [Thesis fully internal (DIV), University of Groningen]. s.n.

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Oral controlled release matrix tablets: concept and literature review

2.1 Background

The oral route is the most frequently used route for administration of drugs. Tablets form by far the majority of oral dosage forms [1]. Important reasons for their popularity are their convenience of application (patient compliance) and the ease of preparation on an industrial scale.

The majority of oral tablet formulations represent the so-called immediate release (IR) dosage forms. Plasma concentration of a drug administered with an IR dosage form generally rises quickly, peaks, and then declines. If the elimination of the drug is fast, this results in only a short period during which the plasma concentration of the drug is within the therapeutic window [2] (figure 2.1). For a successful pharmacotherapeutic treatment, optimal control of the plasma level of the administered drug is a prerequisite. For most drugs, plasma levels should ideally be constant and within the therapeutic window throughout the period of treatment as to avoid adverse side effects due to high toxic peak concentrations as well as to avoid periods of ineffectiveness due to subtherapeutic plasma levels.

Conventional IR dosage forms have to be administered several times a day as to maintain a therapeutically effective plasma level of the drug, which is a major drawback in terms of patient compliance [3]. Still, oscillating plasma concentrations may result in alternating periods of toxicity and ineffectiveness, despite a proper choice of the dosing regimen plasma.

In order to improve the therapeutic efficacy of oral drug administration, and to overcome many of the drawbacks of conventional IR dosage forms, pharmaceutical R&D within academia and industry has focussed on the development of oral controlled release technologies and novel release-controlling excipients.

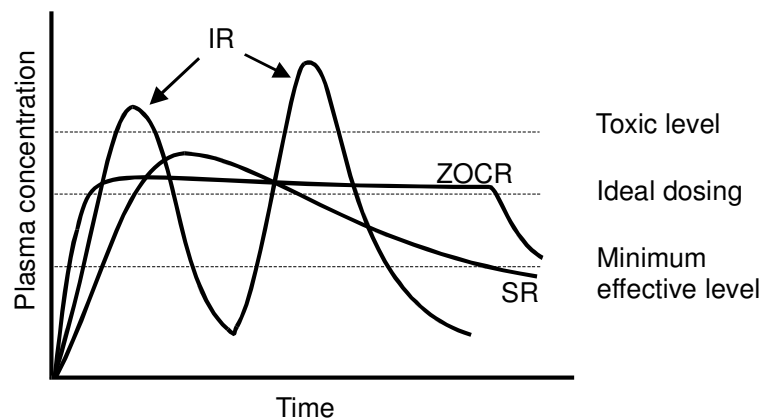


Figure 2.1 Characteristic representation of plasma concentrations of a conventional immediate release dosage form (IR), a sustained release dosage form (SR) and an idealised zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose).

The United States Pharmacopoeia definition of a controlled release or modified release system, as it is also called, is that:

‘the drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by onventional dosage forms....’

Oral controlled release formulations overcome many of the drawbacks of conventional IR dosage forms. Contrary to conventional IR dosage forms, CR tablets are not associated with alternating periods of toxic levels and sub-therapeutic concentrations, thereby improving the therapeutic efficacy and avoiding toxic side effects [4]. This makes controlled release especially suitable for (1) drugs which have plasma peak levels associated with adverse side effects and (2) drugs with a short terminal half-life of elimination. The reduced side effects and lower frequency of administration of CR tablets represents increased comfort and improved patient compliance and more reliable tablet intake, which is especially important for patients which are subject to a chronic medication regimen [3,5-7]. Furthermore, controlled release formulations have the potency to reduce hospitalisation costs, since self-administration is relatively easy.

Using controlled release formulations, many drugs, both known commercially available pharmaceutical products and new molecular entities, can be delivered in ways that not only improve safety and efficacy but, in some cases, permit new and more effective therapies. It is more and more believed that modification of release

patterns (e.g. pulsatile, continuous) is an effective method to improve therapeutic responses.

When addressing the need for novel oral controlled release technologies, the time and costs associated with the process of drug development should be taken into account. Today, the total time of the drug discovery and development process of a new NCE drug generally exceeds 10 year and the development costs have rapidly increased over the last decade to approximately \$600-800 million in 2004 [8]. In spite of the almost 100% increase in investments per drug development program over the last 10 years, the annual number of NCE drugs reaching the market has not increased during the last decade. Despite the availability of advanced screening technologies, discovery of new drug leads suffers from disappointing results. Additionally, an increasing number of pharmaceutical development programs are set on hold during (late) clinical stages due to failure to collect sufficient evidence for clinical efficacy. Even in post marketing surveillance (PMS) stages new products have to be withdrawn from the market due to unacceptable adverse side effects. For the drugs that do reach the market, in order to gain a positive return on the overall investment, the annual product sales need to be huge in the short period (~10 years) that is left between market introduction and patent expiry.

Line extensions of successful first generation products form an interesting alternative for the pharmaceutical industry. The development costs and risks associated with the development of line extensions are substantially lower as compared to NCE drugs. Line extensions based on advanced controlled release technologies may provide additional patent protection, which is an important issue from a product life cycle management (LCM) point of view. For the generic industry, controlled release technologies based on cheap excipients and cost effective manufacturing processes provide an interesting option as generic products bioequivalent to high priced originators may be produced at low costs.

Due to the above mentioned market drivers the demand for novel, safe and reliable oral controlled release technologies is continuously increasing. However, it has to be realised that substantial investments in both toxicological and clinical testing of new controlled release technologies and excipients used therein are required before they will eventually be approved by the regulatory authorities and accepted by the risk-mitigating pharmaceutical industry.

From this point of view, new excipients of natural origin or synthetic materials with proven biological safety form an interesting class of materials. The introduction of new excipients onto the market is highly facilitated if these excipients are covered by existing monographs or if drug master files are available. Registration of new drug products containing such excipients is relatively easy and does not require additional expensive toxicological investigations. On the other hand, if safety has not been recognised yet, huge additional costs will have to be made before the regulatory authorities will accept a drug product containing these excipients.

The two excipients discussed in this thesis, amylopectin and poly(DL-lactide), fulfil these pre-requisites. Amylopectin is an attractive alternative over existing excipients because of its starch-derived nature and its proven safety and available Pharmacopoeial Monograph (USP/NF, pregeletinized starch). Poly(DL-lactide), due to its GRAS status (generally recognized as safe) and available drug master files (DMF) is already widely used in medical and pharmaceutical products.

2.2 Concepts in oral controlled release

The idea behind oral controlled release technologies is that plasma levels of the drug can be optimized by controlling the delivery of the drug from the formulation into the gastro-intestinal tract. Control can be achieved with a 'simple' sustained release dosage forms which releases the drug at a specific rate over a predetermined period of time. In the case of an inherently short-acting drug, a useful and reliable prolongation of the pharmacological effect is often sufficient, and this was the idea behind many CR products developed in the 1980s. It is still a major objective for drugs used in conditions where compliance is a problem. For many drugs, however, to achieve an optimal therapeutic effect, not only the rate of drug release from the dosage form is important, but also the site in the gastro-intestinal tract (e.g. stomach, duodenum or colon) at which the (majority of the) drug is delivered. Both the 'simple' oral sustained release systems as well as the generally more advanced site-controlled drug delivery systems will be addressed below.

Oral modified release dosage forms can be classified in different ways. One way is to distinguish between single-unit dosage forms such as tablets and capsules, and multiparticulate dosage forms such as pellets or beads. According to Caramella et al. [9] oral sustained release technologies may be classified according to different criteria including the type of release (e.g. delayed, slow, prolonged, pulsed, repeat-action, etc.), the release mechanism (e.g. diffusion, dissolution, etc.) or the type of technological 'system'. Combining the classification methodology used by Caramella et al. and Haan et al. [5] controlled release products can be classified as follows:

- reservoir systems including enteric coated tablets, capsules, coated granules and microcapsules
- osmotic systems
- ion-exchange resins
- matrix systems

Matrix systems can be further subdivided into:

- monolithic matrix tablets
- gel-forming hydrophilic matrix tablets
- erodible (hydrophobic) matrix tablets

Below the different types of matrix tablet systems will be further reviewed.

2.2.1 Inert monolithic matrix tablets

Probably the simplest method of obtaining sustained release of a drug from an oral dosage form is incorporation of a drug in an inert matrix [10]. In this respect inert means non-interacting with the biological fluids. The application of inert polymer matrix tablets dates back to the mid 50's when the first matrix tablets containing non-toxic synthetic resins as a 'firmly coherent skeleton structure' in which the soluble drug powder was embedded, were introduced [11]. Since the introduction of plastic matrix tablets, these preparations have gained considerable use. Commercial plastic matrix tablets include the Duretter[®] of AB Hässle (Sweden) [12,13] and Gradumet[®] [5]. The main reason for its popularity is that drug release from plastic matrix tablets is independent on the state and condition of the digestive juices, which may show large inter- and intra-patient variability (pH, viscosity) [10].

During its transit through the gastro-intestinal tract, the porous matrix tablet does not disintegrate like conventional tablets, but remains intact and the skeleton can be recovered in the faeces. The materials used in the preparation of these inert matrices are predominantly inert (insoluble) polymers and lipophilic compounds. The first polymers to be used for the preparation of matrix tablets were (semi-)synthetic polymers such as polyethylene, polyvinylchloride, polymethyl methacrylate, polystyrene, polyvinyl acetate, cellulose acetate and ethylcellulose. The fat compounds used included carnauba wax, hydrogenated castor oil, and tristearin [9].

Major drawback of most of the 'inert' polymeric matrix tablets were their inherent first order drug release characteristics, their poor direct compression characteristics and the problematic cleaning of agglomeration equipment used for the preparation of agglomerates with the required compression characteristics. Nowadays, research in this area focuses on natural biopolymers such as cellulose and starch derivatives, some of which can be considered as semi-inert (ethylcellulose).

■ Mechanism of release of inert monolithic matrix tablets

Release from inert matrix tablets occurs via a leaching mechanism (figure 2.2). Drug particles dispersed in the polymer matrix dissolve in the penetrating gastro-intestinal fluids and are released from the tablet by diffusion through the porous network of already existing pores and pores that are created by dissolution of the drug particles.

At drug loadings exceeding approximately 10-15 vol.%, a continuous structure connecting all drug particles exists (percolating drug network). At considerably lower loadings, a particular fraction of the drug may be completely surrounded by the polymer matrix (trapped fraction), which would result in incomplete release. Higuchi and co-workers developed a model describing release of drugs in a homogeneous ointment base [14].

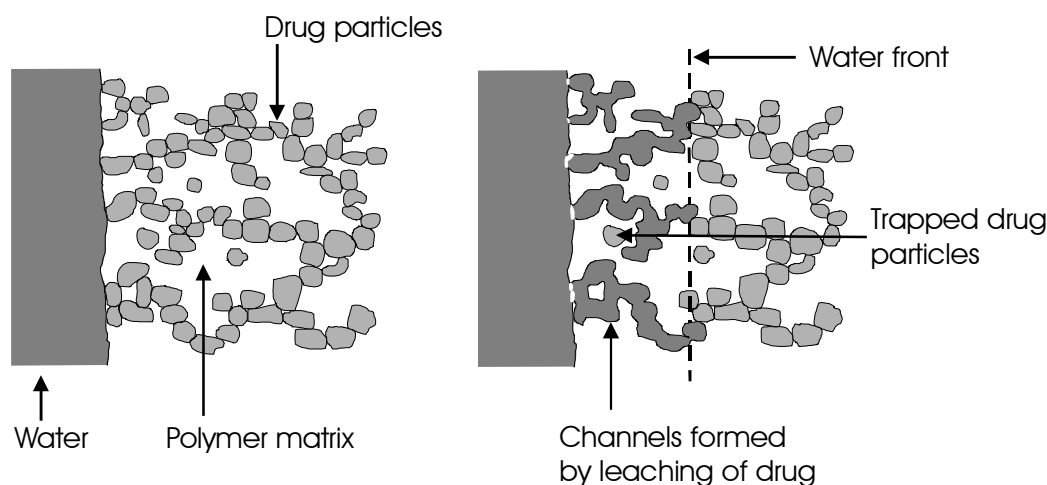


Figure 2.2 Schematic representation of a leaching-based release mechanism. It has to be noted that this is an idealized representation as pores which are normally present in a compacted powder blend are not taken into account (adapted from Baker) [15].

Modification of this equation enabled the prediction of drug release from a porous granular matrix with connecting capillaries [16]:

$$Q = \sqrt{\frac{D \cdot \epsilon}{\tau}} (2C_d - \epsilon \cdot C_s) C_s \cdot t \quad (2.1)$$

In this model, Q is the amount of drug released per unit surface area and C_d and C_s are the drug load and the solubility of the drug, respectively. A porosity factor (ϵ) was introduced to correct for the volume fraction of the matrix that is filled with water. The model further required a tortuosity factor (τ) to correct for the increase of the diffusional pathway of the drug in the porous structure. Since release is based on diffusion, during the ongoing release process, the diffusional distance of drug molecules increases, and consequently, the drug is released according to a first order process, i.e. the fractional release is proportional with the square root of time. A wide range of studies, using the Higuchi model, have been performed to describe drug release from plastic matrix tablets [17-20]. Fessi *et al.* applied the model to matrices with high contents of soluble drug substance, finding τ values of approximately 2 [20]. A study by Gurny *et al.* showed that sustained release of water-soluble drugs from porous ethylcellulose polymer matrices can be divided in a dissolution-controlled and an diffusion-controlled stage [21]. Ethyl cellulose matrix tablets have been applied for the release of a range of drugs including acetaminophen [22] and propranolol HCl [23].

Since the pore structure of the matrix controls water uptake [24,25] and drug release, variation of several parameters such as compaction pressure [26] and speed, plasticiser (moisture!) fraction, fraction of soluble compounds, and fraction

channelling agents will result in different porosity and pore structure and modification of the release rates. For drugs with a rapid elimination that are produced into a inert monolithic matrix CR formulation to reduce the dosing frequency, however, the first order release kinetics are a disadvantage since it may still result in periods with subtherapeutic plasma levels. When the sustained release formulation is used to reduce the plasma peak level (to reduce side effects) this disadvantage is of lesser importance.

2.2.2 Solvent activated matrix tablets

The use of solvent-activated matrix tablets as a method to obtain zero order release, i.e. constant release rates over an extended period, was first proposed by Hopfenberg [27] and has been extensively investigated since then [28-30]. Solvent-activated drug delivery systems is a collective term comprising those systems in which the interaction between polymer and water is responsible for achieving controlled release. The interaction with water may include plasticisation, swelling, dissolution, erosion or degradation of the polymer. The two most important types of solvent activated matrix tablets are gel-forming hydrophilic matrix tablets and erodible matrix tablets.

■ Gel-forming hydrophilic matrix tablets

Gel-forming hydrophilic or swellable matrix systems are homogeneous or heterogeneous systems in which the drug is dispersed in a swellable hydrophilic polymer. These systems have been widely studied by researchers since they offer the possibility to obtain a constant drug delivery over an extended period of time. Drug release is a function of the polymer characteristics.

Upon swallowing gel-forming hydrophilic matrix tablets, the hydrophilic polymer is plasticized by the aqueous gastro-intestinal due to which it undergoes macromolecular chain relaxation and volume expansion. Consequently, upon penetration of the gastro-intestinal fluids into a tablet, a sharp front can be distinguished which separates a dry, glassy core from a hydrated and rubbery gellayer. Release is governed by diffusion of the dissolved drug through the swollen gel-layer and generally shows a burst effect, caused by dissolution and leaching of drug particles present at the surface prior to formation of the release-controlling gel. The mechanism of drug release from swellable devices is determined by the relative position of the rubber-glass interface, the rate at which it penetrates the tablet, the diffusion coefficient of the drug and the erosion rate of the gel. When the penetration rate is high as compared to the drug diffusion rate through the swollen gellayer, release is controlled by the diffusion rate of the drug through the gellayer and a diffusion-controlled (Fickian) release mechanism is observed. If diffusion of the drug through the gellayer is fast as compared to the water penetration rate, release of the incorporated drug is governed by the penetration rate of the interface and zero-order

drug release with constant release rate may be achieved. Several dimensionless parameters have been developed to characterise drug release from swelling-controlled dosage forms. The Deborah number (De) represents the ratio of the characteristic relaxation time of the swelling polymer (τ) relative to the characteristic diffusion time of the water into the polymer (θ) [31-33]. The swelling interface number (Sw) represents the ratio of the solvent penetration front velocity (ϑ) to the rate of drug diffusion through the swollen polymer [30,34]:

$$De = \frac{\theta}{\tau} \qquad Sw = \frac{\vartheta \cdot \delta(t)}{ID} \qquad (2.2)$$

where ID is the diffusion coefficient of the drug in the swollen layer and $\delta(t)$ is the thickness of the latter. In order to characterise release behaviour, it is necessary to determine both De and Sw since neither of these values is sufficient by itself. Peppas and co-workers have extensively investigated diffusion- and solvent controlled drug release from swellable polymeric devices with various geometries [35,36]. Release from swellable tablets can easily be analysed by the following simple equation:

$$\frac{M_t}{M_\infty} = kt^n \qquad (2.3)$$

where M_t/M_∞ is the fractional drug release, k is a constant representing structural and geometrical characteristics of the device, and n gives the type of release mechanism. When the rate at which the penetration front moves inward into the glassy core is high as compared to the diffusion rate of dissolved drug molecules through the swollen gellayer, release is controlled by the diffusion rate of the drug through the gellayer and a Fickian diffusion controlled release mechanism with $n \approx 0.5$ is observed. If diffusion of the drug through the gellayer is fast as compared to the solvent penetration rate, release of the incorporated drug is governed by the penetration rate of the interface. For dosage forms with a slab geometry, this leads to zero-order release ($n = 1$), which is also called non-Fickian, Case II or solvent penetration controlled release. Release profiles with intermediate n -values ($0.5 < n < 1$) are classified as anomalous.

Poly(hydroxyethyl methacrylate) (p(HEMA)) is probably the most widely studied gelforming polymer in oral controlled release. Sustained release from p(HEMA) based devices has been reported for tripeleneamine HCl [37] and theophylline [38]. Release of theophylline from poly(HEMA-co-MMAⁱ) [30,39,40] and poly(HEMA-co-NVPⁱⁱ) copolymers [39,41] could effectively be modified by variation of the copolymer composition.

ⁱ MMA = methyl methacrylate

ⁱⁱ NVP = n-vinyl pyrrolidon

Because of their swelling capacity, several cellulose derivatives are applied as swelling-controlled drug delivery excipients. The most widely applied are probably carboxymethylcellulose sodium (CMC) and hydroxypropylmethyl-cellulose (HPMC) [42-45]. A variety of different molecular weight (Mw) grades HPMC polymers are available. The system is known to be extremely robust. Since the initial tablet porosity does hardly affect drug release due to the rapid formation of a release controlling gel-layer, wide tolerances can be permitted in production factors such as compaction pressure [46]. This is considered a major advantage over leaching-based release from inert monolithic matrix tablets. For most of the HPMC-based controlled release tablets, release is controlled by diffusion through the gel-layer. However, by a proper choice of the polymer Mw, the viscosity and erosion/dissolution characteristics of the gel-layer may be modified [43] in such way that pseudo or near zero-order release can be achieved. Ford et al. analysed the release of several drugs from HPMC K15M [47]. For promethazine HCl, aminophylline, propranolol HCl and theophylline n-values of ~ 0.67 (anomalous release) was found, whereas for the poorly soluble drugs diazepam and indomethacin, n-values of 0.82-0.9, indicating nearly zero-order release, were obtained.

Other swellable polymers which have been applied in swelling-controlled oral drug delivery systems which show solvent controlled release are guar gums [48], poly(ethylene oxide) (PEO) [34,49], poly(vinyl alcohol) (PVA) [50,51], ethylene-vinyl alcohol copolymers (EVA) [52] and dextrans [53]. The dissolution and erosion behaviour of some of the latter polymers in water plays an important role in the release rate and release profile of the incorporated drugs.

Erodible polymers such as polyanhydrides offer another interesting material platform for zero-order drug release. Like several HPMC grades, upon water penetration, polyanhydrides form a gel-layer which erodes at a specific rate. By choosing the right polymer composition the thickness of the gel-layer may remain constant with time resulting in a constant release rate until depletion of the drug.

2.2.3 Site-controlled oral drug delivery systems

Important factors affecting the bioavailability of drugs are the gastric retention time of the dosage form and site of absorption. Some drugs are well absorbed from all regions of the gastro-intestinal tract, while others are poorly absorbed from the lower parts of the intestine or have stability problems in gastric fluids [54]. The awareness of the potential therapeutic benefits of site-specific delivery of orally administered drugs is growing. The gastro-intestinal tract can be divided into several regions (fig 2.3) differing in pH, motility, mucus viscosity and surface tension, enzyme and bacteria concentration, etc.

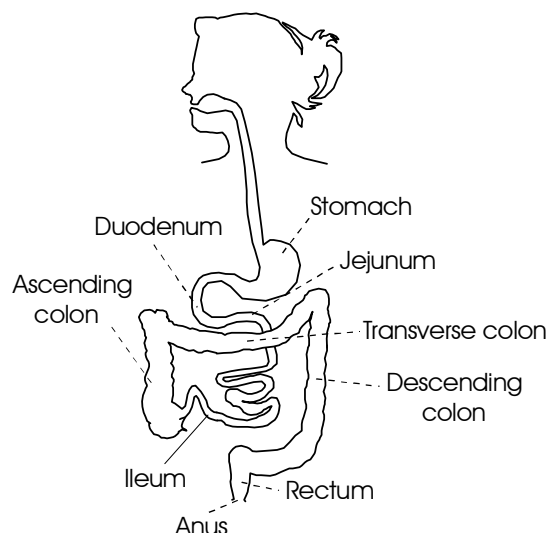


Figure 2.3 The gastro-intestinal tract and potential sites for drug delivery.

| | Transit time (h) | | pH | |
|-----------------|------------------|-----------------|---|-------|
| | pellets | tablets | fasted | Fed |
| Stomach | 0.5-1 | 0.5 | 3-4 | 1.5-3 |
| | 3.6 (1.5 - 5) | 9.6 (3.3 - 14) | | |
| Small intestine | 3.1 (1.5 - 5.7) | 2.0 (1.0 - 3.3) | ± 5 proximal part ± 7.5 ileocecal junction | |
| Colon | 28 (10 - 55) | 15 (3.8 - 26) | ± 6.4 ascending colon ± 7 descending colon | |
| Total | 35 (10-55) | 26 (9.5-42) | | |

Table 2.1 Average GI transit times (fed conditions) for pellets (0.4-0.6 mm, 1.2-1.3 g/cm³) and, between brackets, non-disintegrating round tablets ($\varnothing = 9$ mm) (adapted from Van den Mooter [55] and Abrahamsson [262]).

There is an enormous potential of polymers with specific properties which can be used to control the site at which drugs are released from dosage forms in order to affect the pharmacokinetics and improve the therapeutic efficacy of the drug.

Concepts in site-controlled oral drug delivery systems include:

- pH-sensitive dosage forms, including enteric coated systems
- gastro-retentive systems
- colon targeting

■ pH-sensitive dosage forms

Enteric coated tablets probably form the simplest form of site-specific oral drug delivery. They have been designed to protect gastric fluid-labile drugs during transit of the acidic stomach and to release their content after having entered the duodenum and for drugs that are irritating for the stomach mucosa (e.g. NSAIDs). Enteric coatings generally consist of polymers containing acid groups, which make them insoluble at low pH, but soluble at higher pH (e.g. cellulose acetate phthalate, methacrylic acid copolymers). A second coating underlying the enteric coating can be added to provide sustained release.

Another technique to protect gastric fluid-labile drugs during transit of the stomach is by the use of pH-sensitive hydrogels. Dong *et al.*, for example, prepared thermal and pH responsive hydrogels for delivery of digestive proteins to the small intestine of patients suffering from pancreatitis [56]. The gels consisted of silicone rubber domains in a thermally reversible, lightly cross-linked poly(N-isopropyl acrylamide) hydrogel matrix, which also contained small amounts of pH-sensitive acrylic acid groups. At gastric pH (1.4) the gels do not swell, thereby effectively protecting the incorporated amylase, whereas at enteric pH (7.4) the polymer swells forming a macroporous hydrogel from which the incorporated amylase is easily released. In spite of their limitations, pH sensitive delivery systems are commercially available for mesalazine (5-aminosalicylic acid) (Asacol® and Solafalk®) and budesonide (Budenofalk®) and EntoCort® for the treatment of ulcerative colitis and Crohn's disease, respectively [57].

■ Gastric retentive drug delivery systems

Many drugs show optimal absorption in the duodenum. The bioavailability of many drugs could be improved and become more predictable if dosage forms could be retained in the upper GI tract for extended periods of time or if the position of the delivery system in the duodenum could be controlled. Types of drugs that could benefit from gastric retentive systems include

- Drugs acting locally in the stomach
- Drugs that are primarily absorbed in the stomach or in the duodenum (e.g. acyclovir, levodopa)
- Drugs that are poorly absorbed at alkaline pH
- Drugs absorbed rapidly from the GI tract
- Drug that degrade in the colon

Various attempts have been made to prolong the retention of the dosage form in the stomach as a way to increase the overall retention time in the GI tract. Approaches used in the development of gastric retentive dosage forms include:

- floatable dosage forms

- Size expansion systems
- bioadhesive and mucoadhesive systems
- high density pellets
- magnetic systems

Floatable dosage forms

Among the dosage forms showing gastric retention, floatable systems [54,58-60] are the most widely studied. Floatable systems are capable of floating on the gastric contents due to their (1) low overall density, which results from the use of low-density materials (e.g. oils, fats, low density foams) [61,62], (2) the use of 'hydrodynamically balanced systems' (HBS), (3) entrapped air (e.g. highly porous coated spheres or capsules) or (4) effervescent gas generating systems, generally based on carbonate compounds [63].

HBS systems are able to maintain their low apparent density while the polymer hydrates and builds a gellayer at the outer surface [64]. The drug is released progressively from the swollen matrix, as in the case of gelforming hydrophilic matrix tablets. HBS systems which may be based on hydroxypropyl-methylcellulose [65] remain buoyant for several hours and have been found to prolong the residence time of the dosage form in the stomach as compared to other dosage forms [66,67]. This approach was used to optimise the therapy of drugs which had local action in the gastric mucus or to enhance the absorption of drugs, which are better absorbed in the upper part of the intestinal tract. The drug will be slowly released from the system in the stomach, leave the stomach and subsequently have the whole of the small intestine available for absorption. Madopar® is a capsule-based HBS system containing 200 mg levodopa and 50 mg benserazide. Following dissolution of the gelatin shell, a matrix body is formed consisting of the active drug and other substances. The drug is released as successive boundary layers of the matrix dissipate. Valrelease®, a floating capsule containing diazepam is used as a once-a-day dosage forms [68].

For a proper achievement of retention, floatable systems should be administered after a meal [69]. However, in quite a number of studies, floating was found not to affect the gastric residence time [58,65]. The presence of food in the stomach was found to be the major factor in determining the gastric emptying of dosage forms [65]. Furthermore, even highly floatable systems will be cleared from the stomach at the end of the digestive phase by the so-called interdigestive housekeeper wave.

Size expansion systems

The stomach is a size-filtering system and so it would be ideally suited to retaining a DDS that is larger than the pylorus [68]. However, dosage forms should be small enough to be taken orally. Several size expandable systems have been investigated

for their suitability as a gastric retentive system. Depomed, Inc. has developed a swellable tablet that achieves sufficient size to resist gastric emptying, while simultaneously providing controlled drug release. Metformin GR™ and Ciprofloxacin GR™ are two products based on this technology. A gastro-retentive form of the OROS technology (Alza Corp.) showed prolonged gastric residence time of more than 12 hours in dogs, but only 33 minutes in humans [70]. Patents for unfoldable or extendible systems are held by Pfizer and Merck.

Superporous swellable hydrogel systems have been developed and extensively studied by the group of Park and are now marketed by Kos Pharmaceuticals. Superporous hydrogels contain densely concentrated small pores that produce capillary channels that absorb water quickly. This rapid absorption results in dramatic swelling that is much faster than a conventional hydrogel [68,71,72]. By modification of the composition of the poly(acrylamide-co-acrylic acid) based hydrogels, the swelling and superabsorbent properties are controlled [68,73-75].

Biomucoadhesive systems

An alternative method of increasing the gastro-intestinal transit time is by the use of bio(muco)adhesive delivery systems, which interact with the viscous gastro-intestinal mucus layer in such a way that they are locally retained [54,76-78]. The intestinal mucus is a highly swollen glycoprotein network that consists of a peptide backbone with oligosaccharide side chains containing hydroxyl and carboxylic groups and holds a varying amount of water. Furthermore, the mucus contains sialic acid ($pK_a = 2.6$) and sulphate groups [79,80].

Bio(muco)adhesive excipients are generally highly swellable hydrophilic polymers, which are claimed to interact with the glycoproteins in the mucus layer. Due to this, dosage forms containing these polymers often combine bio(muco)adhesiveness with a positive buoyancy. The adhesiveness originates from penetration of dangling polymer chain ends into the mucus layer, electrostatic interaction and interfacial interaction of functional groups. Polymers which are claimed to exhibit bio(muco)adhesive properties include sodium carboxymethylcellulose, acrylic acid polymers (Carbopol 934P and polycarbophil), hydroxypropylmethylcellulose, copolymers of vinylpyrrolidone and vinylacetate, poly(methyl methacrylate) (Eudragit E hydrochloric acid salt) and cationic chitosan, sodium alginate, gelatine, pectin and lectin. Polyanions with a high charge density appear to be highly active and among the various anions evaluated, it was found that the polymers containing carboxylic groups, such as carboxymethylcellulose and polyacrylic polymers, show a high level of bioadhesion [81]. Harris *et al.* investigated the feasibility of using bio(muco)adhesive polymers to extend the GI transit time in rats and humans. Among the polymers investigated, polyacrylic polymers are most likely to be of use in delaying gastrointestinal transit [82,83]. However, the major delay is due to an increase in the gastric residence time and not an increase of intestinal transit time [84].

In another study it was found that adhesion of negatively charged polymers on mucosa was weaker than that of positively charged polymers [85]. Consequently, positively charged polymers such as cationic chitosan are retained to a larger degree than negatively charged polymers [86] due to the favourable interaction with the negatively charged carboxylic and sulphate groups of the mucus.

Lectin-based bioadhesive formulations have been investigated by the group of Lehr [87-89]. In contrast to the generally used mucoadhesive polymers, lectins specifically recognize receptor like structure of the cell membrane and therefore bind directly to the epithelial cells themselves (cytoadhesion) rather than to the mucus gel layer. In vitro, tomato lectin was found to bind strongly to rat intestinal mucosa, but in vivo, no significant increase of the intestinal transit time of lectin could be found, most probably because of binding of the lectin to the constant turnover of the intestinal mucus. The use of lectin targeting to the GI tract to reduce transit time of pharmaceutical formulations has to date had limited success. However, lectin could be used to enhance drug absorption via the intestinal mucosa, and because of their high specificity, lectin may well have the potential for targeting of drugs specifically to diseased cells in the colon.

■ Colon-specific drug delivery systems

The colon is an area that is vulnerable to a number of diseases including ulcerative colitis, Crohn's disease, irritable bowel syndrome and carcinomas [57]. Treatment of these diseases with a colon-specific drug delivery system provides an interesting alternative over systemic drug administration because of lower dosing and fewer systemic side effects. Furthermore, for peptides or proteins and many drugs that are degraded or poorly absorbed in the upper gut, the colon provides a novel route for systemic administration.

Basically, four types of colon-specific DDS can be distinguished:

- pH-dependent delivery
- time-dependent delivery
- pressure dependent delivery
- bacteria dependent delivery

The concept of pH-dependent delivery has been described above. Colon-specific pH-dependent DDS are similar to pH sensitive DDS that deliver the drugs to the small intestine, although the polymers used for colonic targeting have a higher threshold pH at which they start to dissolve [90]. Due to significant inter and intrasubject variability in gastro-intestinal conditions such as pH, electrolyte concentration and transit time, pH dependent colon specific DDS show large variation in their performance [57]. Time-dependent colon-specific DDS such as the PulsincapTM (see chapter 11) or other enteric coated timed release systems [91] suffer from the same problem. Ethyl-cellulose-based capsules have been used as an intestinal pressure-

controlled colon delivery system [92]. Pressure dependent DDS are based on the concept of resisting the low upper GI tract muscular contractive pressure and rupturing in response to the high pressure in the colon. Again, inter and intrasubject variability in gastro-intestinal conditions and the influence of fed state seem to withhold such a system from widespread application.

Excipients that are stable in the stomach and intestine, but are susceptible to degradation by bacterial enzymes in the colon provide an alternative method for colon-specific drug delivery. Many so-called azo-bond-based polymers, with a cleavable azo-bond have been developed for bacteria-dependent drug delivery [55,93,94]. Other polymers used include amylose, chitosan, dextran [53,95,96], guar gum, inulin [97] and pectin [98-100].

2.3 Starch-based controlled release excipients

Among the variety of polysaccharide-based excipients used in pharmaceutical dosage forms, starch is one of the most widely used. Starches have many properties that make them an interesting class of materials to be applied in pharmaceutical dosage forms.

Most natural starches consist of two polymers of glucose, i.e. essentially linear amylose and branched amylopectin. The amylase:amylopectin ratio varies depending on the type and source of the starch. Amylose is solely composed of glucose units linked by α -1,4 glycosidic bonds, whereas the glucose units in amylopectin are linked by α -1,4 and α -1,6 glycosidic bonds. The glucose units with an α -1,6 glycosidic linkage are the branching points [101-103].

Starches are classified as safe and non-toxic compounds for peroral administration. A number of pharmacopoeial monographs exist, which makes the introduction of physically modified types of these starches much easier as compared to excipients for which no monographs exist and of which safety has not yet been established. This can be considered as a tremendous advantage. Furthermore, native starches are widely abundant and available from a variety of natural sources (e.g. potato, rice, corn, wheat, tapioca) at relatively low costs. Native starches and physically, chemically or enzymatically modified starches cover a variety of structures, which each have their own specific physical characteristics regarding parameters such as solubility, swelling behaviour (viscosity, gel rheology), temperature and pH dependency of solubility and swelling characteristics, film-forming properties, biodegradability, glass transition temperature, hydrophilicity, etc. (Bio)chemical modifications include any reaction of the hydroxyl groups such as esterification, etherification or oxidation [104,105] and (enzymatic) hydrolysis of the glycosidic bonds [106]. Important parameters of polysaccharide modification are the type of substitute, the degree of substitution (DS) and the polymerization degree (DP). A drawback of (bio)chemically modified starches is that they are generally not covered by existing pharmacopoeial monographs or drug master files.

In contrast to the well-established application of starch-based products as diluents, filler/binders and disintegrants [107], the use of (modified) starches as controlled release excipients in pharmaceutical drug delivery systems is still limited today.

2.3.1 Pregelatinized starches

Pregelatinised starches have been found to be effective as an oral controlled release excipient in directly compressed tablets [108-110]. Pregeletinized starches are produced from starches containing 0-75% amylase by geletinization directly followed by a thermic dehydration process like spray-drying, drum-drying or extrusion and are dispersible in cold water [108-110].

Upon contact with water, the hydrophilic pregelatinised starches swell and form a gel layer which controls release of the incorporated drug. Initial tablet porosity does not significantly affect release characteristics [109]. Thermally modified wheat starch prepared by gelatinisation and freeze-drying can also be used as a sustained release excipient in tablets, but exhibits poor powder flowability [111]. Phosphate and adipate crosslinked modified waxy corn starches containing only the branched anhydroglucose amylopectin, either pregelatinised or not, are not suitable as a sustained release tablet excipient [112].

2.3.2 Amylose

Coatings of a mixture of glassy amylose, which is resistant to pancreatic α -amylase, and ethylcellulose (Ethocel®) have been developed for specific drug delivery to the colon [113]. The coating exhibited gastric and small intestine resistance, but was fermented by enzymes of colonic bacterial origin resulting in delayed controlled delivery of the incorporated drug.

Crosslinked amylose (CLA) has been introduced under the trademark of Contramid™ (Rouger Inc., Canada) as a matrix for sustained drug release [114]. According to the authors, high amylose epichlorohydrin crosslinked starches are a very cost-effective oral controlled release dosage form [115]. *In vivo* results with different drugs showed that inter-patient variability and food effects are low for these amylose-based dosage forms. Marketed products containing this swellable excipient include generic versions of Efidac® (osmotic pump tablet (OROS®), zero-order release) and Voltaren® SR (diclofenac, matrix tablet, Fickian release). By incorporation of α -amylase in the crosslinked amylose matrix, an enzymatic controlled release system (ECDR) was obtained. Both the release rate and profile could be controlled by variation of the enzyme concentration. The Contramid™-ECDR system is claimed to be beneficial for therapeutic agents with reduced solubility [116].

2.3.3 Starch-based hydrogels

Heller and co-workers synthesised a pH-sensitive enzymatically degradable starch-based hydrogel for application in a triggered naltrexone delivery system [117]. The authors proposed a device in which the drug-containing bioerodible polymer matrix (stable at low pH, erosion at pH 7.4) is surrounded by an amylase-degradable hydrogel, which in turn is coated with a layer containing an antimorphine-inhibited enzyme-conjugate. In the absence of morphine molecules, the acidic hydrogel would remain intact, keeping the naltrexone immobilised within the pH-sensitive bioerodible polymer. When external morphine diffuses into the device, the amylase-antibody complex dissociates thereby activating the amylase. The acidic hydrogel is then removed by enzymatic hydrolysis and naltrexone would be released due to erosion of the pH-sensitive polymer at $\text{pH} > 7$. The crosslinked glycidyl methacrylate grafted starch hydrogels synthesised by the authors, however, did not possess the necessary stability and showed progressive swelling prior to activation of the enzyme. Other hydrogels obtained by crosslinking starch/cellulose acetate blends with acrylic acid or methyl metacrylic acid have been mentioned as potential candidates for use as drug delivery carriers [118].

2.3.4 Starch acetate

Starch acetates with degree of substitutions of 1.8-3.0 have been reported to exhibit suitable properties to be applied as sustained release excipients in tablets and agricultural devices [119]. The powders exhibit good flowability and advantageous bond-forming properties. The energy consumption of starch acetates during compaction was claimed to be comparable to the best commercially available direct compression excipients. Using starch acetates with DS 2.6 – 3.0, propranolol hydrochloride was released according to a Fickian release process and macroscopic crack formation was reported to play a role in the release process [120]. Sustained release of the calcium channel blocker diltiazem could be achieved for up to 10-15 hours. A strong positive correlation between in vitro and in vivo drug release was found [121].

2.3.5 Amylodextrin

■ Chemical composition and manufacturing

Amylodextrins are relatively short-chained linear dextrans with a polymerisation degree (DP) of 20-35. Amylodextrins can be prepared by selective enzymatic hydrolysis of the α -1,6 glycosidic bonds of amylopectin, as present for almost 100% in waxy maize starch, followed by precipitation, filtration and washing with ethanol [101-103]. Te Wierik et al. showed the preparation of retrograded products by gelatinization of potato starch in a jetcooker, followed by debranching of the amylopectin fraction under acidic conditions by pullulanase. After completion of the

debranching process the remaining amylase fraction was enzymatically degraded by α -amylase. After separation of the precipitate from the mixture by filtration, the resulting product was dehydrated by washing several times with ethanol.

■ Physico-chemical characteristics

Amylodextrin powders prepared as described above exhibit a high specific surface of $> 1.5 \text{ m}^2/\text{g}$ and extremely good binding properties, giving very strong, low-porosity tablets [122]. The water uptake capacity and swelling degree of amyloextrins is very limited due to their low molecular weight.

■ Use of amyloextrin as an oral sustained release excipient

Nearly zero-order drug release profiles can be achieved with low porosity ($\epsilon < 7\%$) amyloextrin tablets [123,124]. Zero-order (in vitro) release, at least for 8-10 hours was reported for a range of (model) drug compounds with different aqueous solubility such as lidocaine ($C_s = 4 \text{ g/l}$), theophylline ($C_s = 8 \text{ g/l}$), paracetamol ($C_s = 15 \text{ g/l}$), potassium dichromate ($C_s = 117 \text{ g/l}$) and procaine HCl ($C_s = 1000 \text{ g/l}$) [125]. Peroral administration of paracetamol-containing amyloextrin tablets to man showed almost constant plasma concentrations of paracetamol up to 14 hours [124]. The zero-order release characteristics were attributed to controlled solvent penetration into the starch matrix, which was the result of a glass-rubber transition of the amorphous oligosaccharide upon contact with the dissolution medium.

Te Wierik *et al.* also prepared several linear short-chain retrograded pregelatinised potato starch products which were all insoluble and non-swelling in water [125,126], which is in contrast to conventional pregelatinised starches [109]. Drug release from these pregelatinised starches was comparable to release from amyloextrin tablets [126,127]. The tablets became rubbery in water and behind the penetration front cracks formed in the tablet. Drug release could be effectively modified by changing the tablet geometry, compaction force and the incorporation of additional excipients [125].

Beneficial characteristics of amyloextrin include ease of tablet preparation because of its direct compression properties, the potential of a near constant release rate (pseudo zero-order) for an extended period of time and the possibility to incorporate high percentages of drug with different physicochemical characteristics.

2.4 Aliphatic polyesters as controlled release excipients

Aliphatic polyesters are a group of synthetic, non-toxic biodegradable polymers. Poly(DL-lactide) (PDLA), poly(L-lactide) (PLLA), poly(glycolide) (PGA) and poly(glycolide-co-DL-lactide) (PGLA) copolymers are by far the most widely used synthetic biodegradable polymers in pharmaceutical and biomedical applications [15,128,129]. Because of their biocompatibility and bioresorbability [130,131], PLA, PDLA and PGA homopolymers and PGLA copolymers were first investigated for use in resorbable surgical sutures (Dexon[®], Vicryl[®] and Polyglactin[®] 910) [132,133], as well as implantable fracture fixation devices such as bone plates and screws [134-139]. Aliphatic polyesters are generally recognized as safe (GRAS) by the regulatory authorities.

The completely synthetic character of these polyesters is considered an important advantage. Their chemical composition (monomer ratio, tacticity), molecular weight, crystallinity and entanglement density can easily be tailored in order to obtain polymers with the desired physicochemical, thermal, mechanical and (bio)degradation properties. Another advantage includes low batch-to-batch variations (high reproducibility, constant quality) since changes in the feedstock, which are known to affect the quality of biopolymers such as starches and celluloses, do not play a role.

2.4.1 Poly(DL-lactide)

Yolles and coworkers were the first to report the use of PDLA as an erodible matrix in parenteral drug delivery [140]. Since then PDLA and PGLA has been widely investigated for their use in short and long term drug delivery systems, including implants [141,142], micro- and nanospheres [143], microcapsules [144] and sustained-release coating formulations. In the eighties a range of delivery systems were successfully developed for controlled release of narcotic antagonists [145], leutinizing hormone releasing hormone [146], (contraceptive) steroids [147], chemotherapeutic agents [148], local anaesthetics [149], antibiotics, growth factors [150] and antimalaria drugs [151]. Both the drug delivery systems and their potential applications have been reviewed elsewhere [152,153].

■ Manufacturing

Low-molecular weight PDLA and PGLA can simply be prepared by polycondensation of L-lactic acid, D-lactic acid and glycolic acid in the appropriate ratio, yielding low molecular weight polycondensates with low mechanical strength [135]. Higher molecular weight grades poly(lactide) are preferably produced by ring opening polymerization (figure 2.4) of dilactide (cyclic dimer of lactic acid) using a suitable catalyst such as stannous octanoate, Zn and Ti salts or coordinating catalysts like Al-isopropoxide [15,135,154].

The low degradation rate of PLLA and PGA is the reason that research on the application of polyesters in pharmaceutical and biomedical preparations has shifted from these crystalline homopolymers to their amorphous copolymers (PDLA and PGLA). The combination of relatively high degradation rates and good processability have made PGLA copolymers the most widely studied controlled release polymer in injectable (parenteral) drug delivery systems and implants.

■ Application of PDLA as an oral sustained release excipient

The low degradation rate of PDLA homopolymers is considered to be a drawback for its application in a range of long-acting drug delivery systems, such as implants and injectable microspheres. However, it does not negatively affect its applicability in oral dosage forms. On the contrary, the fact that PDLA behaves relatively inert in the gastro-intestinal tract, and that it will slowly degrade into harmless, naturally occurring degradation products after excretion in the faeces, makes it an interesting compound to be applied as a pharmaceutical excipient in tablets, whether as a filler/binder or a release controlling compound.

Direct compression tablets

The first studies of Korsatko in 1982 using PLLA (M_w 40,000) as a direct compression excipient showed that PLLA exhibited poor compaction properties due to its elastic behaviour during compression and that the tablets had low tensile strength and high friability [162]. Release experiments showed that PLLA tablets prepared by direct compression disintegrated rapidly in dissolution media, resulting in fast release of the incorporated celiprolol [163]. The use of fluidized bed techniques or solvent evaporation for granule preparation did not improve the poor sustained release properties of PLLA. Mank *et al.* synthesized PDLA with a low degree of crystallinity both by direct polyesterification of lactic acid (M_w 6,000) and ring opening polymerisation (M_w 25,000) [164]. The latter method yielded threads rather than particles, which could not mechanically be micronized. The polycondensation method, however, resulted in a ductile powder with a mean powder particle diameter of 120 μm , which was suitable for direct compression. The elastic recovery of compacts (post-compaction increase of porosity) during the decompression stage was low, resulting in tablets with low porosities, but tablets did not have high crushing strength. The low crushing strength was attributed to the low molecular weight and low T_g of approximately 30 °C of the PDLA grade used. Release of caffeine and phenazone [165] was nicely sustained and dependent on the solubility, particle size and load of the drugs.

Moll and Köller [166] studied both crystalline PLLA and amorphous PDLA, both with M_w 2,000, as release controlling excipients in matrix tablets. PLLA tablets were easy to handle because of high mechanical strength and almost no friability. *In vitro*, under physiological conditions (pH 1.2-6.8), PLLA matrix tablets yielded sustained

release of the incorporated theophylline. Drug release was hardly affected by pH, but influenced by drug load. Up to drug load of 60% w/w, drug release from both PLLA tablets could well be described by the Higuchi equation. PDLA tablets showed incomplete theophylline release at pH 1.2, due to a loss of tablet pores which was caused by the low T_g of this low M_w PDLA ($T_g \sim 20^\circ\text{C}$), which led to collapse of the matrix and blocking of the pores due to viscous flow of the rubbery polymer in 37°C dissolution medium. Release at pH 7.4 was accompanied by swelling of the matrix, due to increased hydration of free carboxyl groups at these pH-values. The authors concluded that the strong pH dependency of drug release makes low molecular weight PDLA unsuitable for application in peroral controlled release matrix tablets. Brine [167] reported that the addition of certain pharmaceutical excipients (e.g. microcrystalline cellulose, dicalciumphosphate, lactose) considerably improved the retarding properties of low molecular weight PLLA and PDLA ($M_w \sim 3,000$, $T_g \sim 26^\circ\text{C}$). Using additional excipients, the retarding properties of these low molecular weight poly(lactides) were comparable to M_w 30,000 PDLA. The poly(lactides) could be introduced in the formulation by any convenient method such as dry mixing, wet granulation or by applying a solvent system.

(Pseudo)latex dispersions

Chang and McGinity prepared PDLA matrix tablets by introducing PDLA ($T_g \sim 56^\circ\text{C}$) into the formulation either as an aqueous latex dispersion [168], or by dissolving the polymer in methylene chloride [169] and granulating the blend of the pharmaceutical ingredient and excipients with the dispersion/solution to disperse PDLA homogeneously throughout the matrix [170]. Sufficient amounts of polymer (5-15% w/w) had to be added in order to form a polymer matrix capable of retarding the release of the active ingredient (25% w/w). Tablets prepared by both methods disintegrated rapidly unless they were heated above T_g for several hours. Thermal treatment largely changed the physical-mechanical characteristics of the tablets [170,171]. SEM photographs showed that after annealing, the polymer acts as network that prevents disintegration. Due to annealing, the hardness and disintegration time increased, the tablet friability decreased and release of theophylline was retarded (60% released in 48 hours). Omelczuk and McGinity studied the effect of T_g and M_w on drug release from tablets in which PDLA was incorporated according to both methods mentioned above [172]. Drug release from M_w 3,500 was fast due to disintegration of the tablets. The release of theophylline slowed down progressively as the polymer molecular weight increased. Although some swelling occurred due to the presence of 60% microcrystalline cellulose, release was based on leaching obeying the square root of time kinetics of the Higuchi-equation [16]. The initial swelling of the tablets decreased with increasing molecular weight.

Drug release from tablets prepared from aqueous pseudolatex dispersions was significantly faster than that from tablets granulated with the organic solvent. Thermal treatment of the pseudolatex tablets above the T_g resulted in significant

retardation due to stronger compact formation and a more efficient redistribution of polymer throughout the tablet matrix [171]. The compaction properties of acetaminophen/ lactose-monohydrate powder blends improved considerably by incorporation of PDLA (M_w 92,000) as a pseudolatex binder [173]. The tensile strength, indentation hardness and bonding index increased whereas the brittle fracture index decreased. Thermal treatment of the tablets above T_g further improved the bonding index. Matrix formulations containing PDLA as a binder had compaction and retardant properties that were better than tablets containing ethylcellulose or poly(ethyl acrylate, methylmethacrylate) as a binder.

Spray-dried powders

Spray-dried PGLA powders [174] have been used as retardants in matrix tablets for the controlled release of phenobarbitone [175]. Except for very dilute PGLA solutions (< 2% w/v), spray-drying of high molecular weight PGLA yielded threads rather than particles. By spray-drying of lower molecular weight PGLA, porous and almost spherical agglomerates of tiny spheres could be prepared. The powders were ductile, and exhibited high compressibility and moderate polymer hydrophobicity. Contact angles (~ 72 - 78°) were independent of molecular weight, but decreased with increasing glycolide content. Release of phenobarbitone (solubility 1 g/l) showed a significant burst after which zero-order release was observed for 15 to 35 days. Release of phenobarbitone occurred via diffusion through water-filled pores and diffusion through the swollen polymer, according to the authors. Sodium phenobarbitone (aqueous solubility of 1000 g/l) was completely released within 3 hours via a leaching mechanism.

Microporous poly(lactide) powders

Microporous poly(lactide) powders (void fraction 0.3-0.9), prepared by liquid phase separation and solvent evaporation [176] were found to be useful as retardant in oral dosage forms. Tablets were prepared by mixing of drug and microporous polymer powder followed by compaction of the blend. Surprisingly, in some case, drug release rate was found to increase with compaction pressure. Obviously, release from matrix tablets containing microporous PDLA was not related to the penetration rate of water into the tablets.

2.5 Physicochemical aspects of polymeric excipients in relation to drug release from oral tablets

The simplicity of the direct compression process is responsible for the popularity of the matrix tablet prepared by direct compression. Preparation only involves blending of the drug and (polymeric) excipients and subsequent compaction of the powder mixture ('direct compression') by conventional pharmaceutical techniques.

2.5.1 Plasticisation of polymers by moisture

Many amorphous and semi-crystalline pharmaceutical excipients are known to absorb and retain significant amounts of atmospheric moisture. It is well known that this water significantly affects physico-chemical characteristics such as glass transition temperature (T_g), visco-elasticity, powder flowability and chemical stability (degradation) [177]. Moisture sorption behaviour of starches has been discussed in detail by Van der Bergh [178], Zografi [177,179,180] and others [105]. The exact amount of sorbed moisture depends on the nature of the compound, the temperature and the relative humidity. The physical and chemical properties of amorphous polymers are critically dependent on the amount, state and location of water molecules. Water molecules may be adsorbed to the external surface of the solid, absorbed into amorphous regions or condensed into pores. There are few publications on the reduction of the glass transition temperature of hydrophobic amorphous polymers after absorption of small amounts of water. For epoxy resins [181], nylon [182] and poly(DL-lactide) [183] small amounts of water were found to have a marked plasticising effect.

2.5.2 Effect of moisture on compaction behaviour

Since the visco-elastic properties of polymers are significantly different at temperatures above T_g (rubbery state) as compared to temperatures below T_g (glassy state)), it is likely that physical properties of the solid will undergo changes at distinct moisture contents and defined temperatures as a result of a glass transition. Compaction behaviour and properties of the resulting tablet (porosity, tensile strength) have been reported to be dramatically affected when the polymer passes the glass transition and becomes rubbery [184,185]. Compression of a rubbery polymer, for example, results in extensive relaxation during the decompression stage, making it practically impossible to prepare strong compacts. Therefore, in practice, glassy polymers are applied as matrix-forming tablet excipients. Starches, for example, are rigid at low moisture content, whereas they become more ductile at higher moisture content. Moisture facilitates both elastic and plastic deformation of modified starch, due to lowering of the elastic modulus and viscosity of the material [184].

■ Compaction of powder blends

Matrix-type tablets are generally prepared by compression of a powder blend of drug and polymer particles. Several stages can be distinguished in the powder compaction process. Initially, consolidation occurs through particle rearrangement. Further densification of the powder bed occurs through plastic deformation, in case of ductile materials, or through fragmentation, in case of brittle excipients [1]. An important class of polymeric pharmaceutical excipients includes (modified) starches and celluloses, which are amorphous or semi-crystalline and are known to deform plastically during compaction. Due to its plasticising activity, water influences plastic deformation of glassy polymers during compaction. Consolidation of the powder compact is facilitated due to reduction of the yield pressure with increasing moisture fraction. In addition, the lubricating activity of water facilitates slippage of the particles during compression. However, the presence of water adsorbed at the surface of the particles also affects bonding between particles and thus the tablet strength. Above a certain level, the presence of water weakens interparticle bonding. Strong interparticle bonding prevents a tablet from extensive relaxation after ejection from the die. Therefore, if interparticle bondings are weak due to the presence of large amounts of surface water, extensive relaxation will occur resulting in an increase of the tablet porosity. In fact, when tableting at relatively high pressures, final porosity and tablet strength are predominantly the result of relaxation of the powder compact during the decompression stage in die, and after ejection, out of die [186-188]. The maximum degree of densification during compression only plays a minor role. Because of the plasticizing effect of water on amorphous polymer powders, the effect of moisture on the thermal, visco-elastic and compaction properties of amylopectin will be discussed in more detail in chapters 3 and 4.

